3. (Unchanged) A polynucleotide according to claim 1, wherein said spacer comprises a nucleotide sequence as shown in SEQ I.D. No. 10 or SEQ I.D. No. 11.

4. (Unchanged) A polynucleotide according to claim 2, wherein said promoter is selected from an SV4O promoter or an MLV promoter.

B2

5. (Amended) A polynucleotide according to claim 2, comprising at least four HRE repeats linked to the promoter, wherein at least two of the HRE repeats are positioned upstream (5') of the promoter and at least two repeats of the are positioned downstream (3') of the promoter.

6. (Amended) The polynucleotide of claim 7, wherein at least three of the HRE repeats are phosphoglycerate kinase (PGK) hypoxia respones elements (HRE) repeats operably linked to an SV40 promoter or an MLV promoter.

7. (Amended) A polynucleotide according to claim ~~6~~ 5, comprising at least six HRE repeats, wherein at least three repeats are positioned upstream (5') of the promoter and at least three repeats are positioned downstream (3') of the promoter.

8. (Unchanged) A polynucleotide according to claim 1, wherein the HRE repeats are direct repeats.

B3

9. (Amended) A polynucleotide according to claim 1, wherein the HRE comprises the nucleotide sequence of SEQ ID NO:1 or 2.

10. (Amended) A polynucleotide according to claim 1, comprising the nucleotide sequence of SEQ ID NO: 9.

11. (Amended) A polynucleotide according to claim 6, comprising the nucleotide sequence of SEQ ID NO: 3, 4, or 5.

12. (Amendeded) A polynucleotide according to claim 2, operably linked to a nucleic acid of interest (NOI), such that the polynucleotide directs expression of the NOI in a host cell.

13. (Unchanged) A polynucleotide according to claim 12, wherein the NOI encodes HIF-1.

14. (Unchanged) A polynucleotide according to claim 12, wherein the promoter lacks a CAAT box sequence.

15. (Unchanged) A polynucleotide according to claim 12, wherein the host cell is a tumour cell.

16. (previously cancelled)

17. (Unchanged) A polynucleotide according to claim 12, wherein the NOI encodes a polypeptide which is cytotoxic.

18. (Unchanged) A polynucleotide according to claim 12, wherein the NOI encodes a polypeptide capable of converting a precursor into a cytotoxic compound.

B4

19. (Amended) A polynucleotide according to claim 12, wherein the NOI encodes a transcription factor, a metabolic enzyme, a proliferation-regulating protein, or a heat shock protein.

20. (Amended) A polynucleotide according to claim 12, adapted to deliver the NOI to a mammalian cell.

21. (Amended) A polypeptide according to claim 1, disposed in a nucleic acid vector.

22. (Amended) The polypeptide of claim 21, wherein the vector is a viral vector.

23. (Amended) The polypeptide of claim 22, wherein the viral vector further comprises a nucleotide sequence selected from

(i) a nucleotide sequence encoding an inhibitory RNA molecule capable of effecting the cleavage, directly or indirectly, of VHL RNA;

(ii) one or more inhibitory RNA molecules that bind to and prevent VHL RNA processing, expression, or both; and

(iii) a nucleotide sequence encoding a polypeptide capable of inhibiting the binding of VHL to Elongin B, Elongin C, or both.

24. (Amended) The polypeptide of claim 23, wherein said nucleotide sequence (iii) encodes a non-functional derivative of wild-type VHL.

25. (Amended) The polypeptide of claim 22, wherein the viral vector is a retroviral vector.

26. (Amended) The polypeptide of claim 22, wherein the viral vector is an adenoviral vector.

27. (Amended) The polypeptide of claim 22, wherein the viral vector is a lentiviral vector.

28. (previously cancelled)

29. (previously cancelled)

30. (previously cancelled)

B5

31. (Amended) A method of producing a viral strain which method comprises introducing a polynucleotide of claim 2 into the genome of a virus.

Election:

To the extent the Restricted Groups are maintained and not recinded for the reasons discussed above, Applicants elect Group I, drawn to polynucleotides comprising at least two repeats of an HRE (SEQ ID NO: 1 or 2), or an HRE/promoter construct (SEQ ID NO: 9), separated by a spacer (SEQ ID NO:10 or 11), and a nucleotide of interest (NOI) such as HIF-1, and to vectors and host cells comprising the polynucleotide.

Should the Restriction Requirement be changed to include Applicant's base claim 1, Applicants elect that Group including claim 1, a polynucleotide comprising at least two HRE repeats separated by a spacer of at least 20 contiguous amino acids.

Improper Restriction:

Applicant's resptectfully assert that the Restriction Requirment imposed on the Applicant's claims is improper, and should be recinded. In particular, the Applicants note the Restriction Groups do not include the subject matter of the applicant's claims, in particular the base claim 1 and its dependent claims 2-11. The Restricted Groups all require the claimed invention to include a nucleotide of interest (NOI), an optional embodiment of the invention that is recited in dependent claim 12. Accordingly, Applicants assert the Restriction is improper and must be recinded.

Further, the Restriction Requirement fails to take into account the unifying features of the claimed invention, and instead divides the claims into eight different groups (I-VIII) on the basis of a type of (optional) nucleotide of interest (NOI), and two groups reciting viral vectors comprising the claimed polypeptide, selecting out as independent groups where the vector is a retrovirus (group IX) and an adenovirus (Group X).

In contrast to the Examiner's statements in the Restriction Requirement, Applicants assert the original claims clearly recite a general inventive concept. The claims have also been amended to assist the Examiner's review of the unifying features of the claimed invention.

Beginning with claim 1, each of the original (and amended) claims requires the claimed polynucleotide to comprise at least two HRE repeats separated by a spacer of at least 20 contiguous nucleotides. Claim 2 requires the repeats to be operably linked to a promoter. Additional dependent claims recite polypeptides that comprise at least four or at least six HRE repeats; specify the disposition of the repeats in relation to the promotor, and provide specific examples (SEQ IDs) of the claimed genus of HREs, spacers, and promoters.

At claim 12, the claimed polynucleotide (comprising at least two HRE repeats and separated by a space of at least 20 contiguous nucleotides) is further operably linked to a nucleotide of interest such that the claimed polynucleotide directs expression of the NOI in a host cell. Dependent claims 13, 15, 17, 18, and 19 provide species of the claimed genus NOI.

Applicants respectfully assert the claims recite a unified inventive concept that claims a unique polypeptide comprising at least two repeats of an HRE separated by a spacer. Additional claims refine the invention and are noted to be in Genus/Species relationship. Accordingly, the issued Restriction Requirement is improper; fails to include all the recited claims; fails to consider the core concepts of the invention; and fails to appreciate the relationships of the independent genus claim and dependent species claims. Applicants respectfully request that the Restriction Requirement be recinded, and that the claimed invention be reconsidered on the merits.

Should the Restriction Requirement be maintained, clarification as to a proper method for rejoinder of the subject matter missing from the Groups is respectfully requested.

Applicants respectfully request a telephone conference with the Examiner and his supervisor to clarify the remarks and amendments made in this paper, and to further prosecution of this case on the merits. The Applicant's representative can be reached at the direct dial number indicated below.

Respectfully submitted,

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